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A FEW MORE WORDS ON STROPHANTHUS.

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"Fas est et ab hoste doceri."

MR PRESIDENT AND GENTLEMEN,—I have to apologise for recurring to this subject so soon. I can only plead in justification the extreme importance of the matter, and the fact that the remarkable contrast that subsists between the action of strophanthus and that of digitalis has not, in my opinion, been sufficiently emphasized upon former occasions. We have been asked to place our faith in strophanthus on the strength of a series of cases in which the employment of that drug was followed by the disappearance of dropsy, and in which the pulse-tracings showed an apparent improvement in the pulse-rate and in the blood-pressure. But, Sir, the like has happened before without either strophanthus or digitalis; nay, it happens daily even now. The symptoms that arise from heart-failure may be relieved in many ways, and recovery from them is no certain indication of the therapeutic value of any drug which may perchance have been coincidentally employed.

The myocardium is a hollow muscle which by its expansion and contraction assists and directs the circulation of the blood; in this action it is aided by valves so placed that, when closed, the whole force of the muscle is expended in propelling the blood onwards. Failure of any of these valves permits the blood to flow backwards as well as forwards, and so places the myocardium at a mechanical disadvantage in regard to the discharge of its function. But the heart works so well within its power that even when such an accident happens suddenly, there is not a falter in the action of the heart, nor any indication in the pulse-tracing of any interruption of the equability of the blood-pressure. This interference with the function of the myocardium ultimately leads to embarrassment of the circulation, but under favourable circumstances this does not happen for many a long day, so that even to old age such a valvular lesion may remain perfectly mute.

But whenever from overwork, privation, or debilitating illness,

the general metabolism is interfered with, the heart suffers; its function is impaired. Like every weak muscle, the enfeebled myocardium reacts to stimuli irritably and irregularly, and does its own peculiar work imperfectly. The ventricles contract less effectually, the arteries are not so well filled, the blood-pressure falls, and venous remora is established, with all the evils that accompany this condition; soakage of all the tissues, with serous accumulation (dropsy) in one or more of the cavities of the body. If we put such a patient to bed, the mere adoption of the recumbent posture at once lowers the pulse-rate by an average of 12 (6-16) beats per minute, and in weakly, ill-fed patients the reduction is sometimes greater. This lowering of the pulse-rate amounts cumulatively to an increase of rest to the heart of over two hours in the twenty-four, and we can readily understand that this rest, coupled with warmth and better feeding, is sufficient to give such a fillip to the general metabolism as enables the heart to recover its tone and to discharge its function more perfectly. The blood-pressure rises, the balance of the circulation as between arteries and veins is restored, dropsy disappears, and the patient is re-established in comparative health.

The record of both the past and present history of medicine shows that many, if not most, of our hospital patients require no other treatment, though recovery may be aided by the judicious use of purgatives, of diuretics, or of such drugs as either diminish the work of the heart or restore the tone of the myocardium. It is evident, however, that those drugs alone are of paramount value which increase the elasticity of the myocardium, and that this action can only be permanent when accompanied by a corresponding improvement in the general metabolism. Thus only can we arrest the organism in its downward career, and place it in such a state of metabolic equilibrium as will ensure the permanence of that improvement which is so often found temporarily to follow the employment of even imperfect and inefficient methods of treatment.

This important action is usually ascribed to all the members of the digitalis group; but though they all possess a certain similarity of action, they vary very much in activity, and they also vary considerably in regard to the structures upon which that activity is exerted, and these two factors have a most important influence upon their usefulness.

The action of *Digitalis purpurea*, from which the group derives its name, is in moderate doses to improve the elasticity of all muscular fibre, and as all the blood passes many times through the heart for once that it passes through any other muscle, the myocardium is powerfully affected, while the other muscles remain practically uninfluenced. In like manner the muscles of the arterioles are also early and powerfully affected, though not to the same extent as the heart, as only the blood going to the district supplied

by these vessels passes through them.¹ The increased elasticity imparted to the myocardium by digitalis enables it to expand and to contract more perfectly, and as, owing to the increased elasticity of the muscles of the arterioles, the arteries empty themselves more slowly, the blood accumulates within them, the blood-pressure gradually rises, and in accordance with Marey's law² the heart's action is slowed. No doubt this is partly due to the action of digitalis on the vagus nerve, but the action on the muscles is sufficient to account for all the phenomena observed, and it is with it we are chiefly concerned. The result of this rise in the blood-pressure is that the secretions are improved, and all the tissues of the body, amongst them the myocardium, are fed with richer blood at a higher pressure, so that metabolism is more perfect and every function more efficiently performed. As the blood accumulates within the arteries the veins are correspondingly emptied; the serous soakage of the tissues is reabsorbed, and the excess of water that thus gets into the blood is removed by the kidneys, so that for a time the urine is increased.

The improved metabolism of the myocardium enables it to discharge its function more perfectly, and to resist successfully all those deteriorating influences to which a weak heart succumbs, any hindrance to the circulation is fully compensated, and despite the existence of a valvular lesion the individual may descend into the vale of years wholly unconscious of the possession of a heart.

All the benefits we obtain from the use of digitalis are inseparably connected with its tonic action; they flow from the power that digitalis has of increasing muscular elasticity, and the improved metabolism of all the tissues, but specially of the myocardium, that follows this. Digitalis is no opium to the heart; it does not relieve by narcotising, but it soothes cardiac irritability by strengthening the cardiac muscle, and it assuages cardiac pain by improving cardiac metabolism, failure of which has been the cause of the pain. These benefits are readily obtained by very moderate doses of the drug, and though great benefit may at times be more rapidly attained by the judicious administration of larger doses, yet the long continuance of even small doses is often followed by the very best results; while the abuse of the drug, so frequently accompanied by distressing, if not alarming symptoms, proceeds upon an entire misconception of the true action of digitalis.

There is only one other member of the digitalis group that has succeeded in obtaining special recognition from cardiac therapeutists, and this is the *Strophanthus Hispidus*, but the action of this drug is so entirely different from that of digitalis that it is

¹ Stockman, *New Official Remedies*, p. 58. London, 1891.

² *Physiologie Médicale de la Circulation du Sang*, p. 206. Par le Dr E. J. Marey. Paris, 1863. Le cœur bat d'autant plus fréquemment qu'il éprouve moins de peine à se vidér.

difficult to see how there can be any comparison between the two. In Africa, its native habitat, *strophanthus* is employed as an arrow poison, and the natives have so great a dread of it that when told that the seeds were employed as a medicine in this country, "they expressed the opinion that the English must be mad to employ so poisonous a substance for medicinal purposes."¹ The action of *strophanthus* on the heart is twofold: in small doses it arrests the heart in diastole, and in large doses it arrests it in systole.² The diastolic type of action seems to be that which alone is useful therapeutically; in it the diastole is prolonged and the contractile energy of the myocardium at the same time increased. The type is thus that of bradycardia, a slow-beating heart sending forward a large blood-wave with each contraction,—not a type of heart usually associated with much vigour of the circulation. This type of heart action is produced only by small doses; and the excessive energy of the drug, the many preparations of *strophanthus* in the market, of varying composition and strength, must introduce an element of uncertainty in its employment that cannot be devoid of anxiety. *Strophanthus* acts three thousand times more powerfully on the heart than *digitalis*;³ so that if some still dread *digitalis* as a dangerous cardiac poison, what must be their feelings towards *strophanthus*. And if it be difficult to select an appropriate dose of a drug of but moderate energy and only one action, how great must be the difficulty in the case of a drug of such excessive potency and possessing a twofold action on the heart. Indeed, whether we regard the uncertainty of its direction or its excessive energy as a poison, it seems difficult to formulate a more forcible indictment against any drug than that presented by a bare statement of the facts recorded against *strophanthus* by its most able investigator and most ardent advocate.

But this is not all. *Digitalis*, as we have seen, acts equally upon all muscular fibre, and only more powerfully upon the heart and muscles of the arterioles because these organs receive from the blood within a given time a larger dose of the drug than the other muscles. The conditions as regards the circulation are permanently similar; and if *strophanthus* acted on all muscular fibre after the manner of *digitalis*, there would be a similar ratio between the action of the two drugs on the heart and on the arterioles, but this is not the case. *Strophanthus* acts three thousand times more powerfully on the heart than *digitalis*, but it acts one hundred times less powerfully than *digitalis* upon the muscles of the arterioles.⁴ There is thus no similarity whatever between the action of the two drugs. From the entire absence of any appreci-

¹ Fraser on "*Strophanthus Hispidus*," *Transactions of the Royal Society of Edinburgh*, vol. xxxv., part 4, p. 974.

² *Ibid.*, vol. xxxvi., part 2, p. 401.

³ *Ibid.*, p. 403.

⁴ *Ibid.*, pp. 438, 453.

able action by strophanthus on the arterioles, the blood flows freely from the arteries into the veins, and any little rise of blood-pressure there may be is entirely due to the systole of the heart. The typical (therapeutically induced) strophanthus heart has a prolonged diastole, so that the arteries have a longer time than usual to empty themselves, and as the ventricle has been filling during this period, its systole sends an unusually large blood-wave into unusually empty arteries—precisely what happens in a case of bradycardia. The momentary rise of the blood-pressure passes rapidly with the blood-wave down the unfilled arteries; it does not, therefore, persist so long as the ventricular systole, and is consequently of shorter duration than even the third of a cardiac cycle. So evanescent a rise in blood-pressure can, however, have no appreciable effect either on general metabolism or upon that of the myocardium. Herein the action of strophanthus differs most essentially from that of digitalis; and from the absence of any improvement in the metabolism of the myocardium, the stimulating action of strophanthus must tend still further to exhaust it instead of strengthening it.

Remembering this, the remarkable twofold action of strophanthus on the heart is easily understood. In large doses it exerts its own poisonous energy unchecked and forces the heart into fatal systole. In minimum lethal or so-called therapeutic doses strophanthus exerts a less powerful stimulation on the myocardium, with a type of action in which slowing of the rate is produced by prolongation of the diastole, and by occasional pauses in extreme diastole, both auricular and ventricular expansions and contractions being at the same time increased.

This tendency to arrest in diastole is not due to any action on the cardio-inhibitory apparatus, because paralysis of the intra-cardiac terminations of the vagus by atropine does not prevent its occurrence. It cannot be due to the action of the drug on the myocardium, as that would imply that in small doses strophanthus is capable of exerting an action on muscle diametrically opposite to that which it undoubtedly exerts in large doses. Accordingly Fraser has suggested that this diastolic type of action is due to a weakening of the excito-motor (katabolic) nerve structures. But so far as I am aware there is no evidence extant to show that even section of the sympathetic, excito-motor, or katabolic nerve does slow the heart's action, or in any way promotes slowing of the heart or its arrest in diastole. Before accepting "weakening of the excito-motor nerve structures" as explanatory of this peculiar type of action, it must therefore first be shown that this "weakening" does occur, and, second, that it is capable of acting as Fraser has suggested. There is, however, another explanation of this diastolic type of action which is in complete accordance with the facts, though it is not an explanation that can be regarded as very comforting to those who regard strophanthus as an important

therapeutic agent. *Strophanthus* undoubtedly exercises a powerful stimulating action on the myocardium, an action which is three thousand times more powerful than that of *digitalis*, which forces the heart into energetic movements of expansion and contraction, but which is not associated with any important rise of blood-pressure, and is unaccompanied by any improvement in the metabolism of the myocardium. A large dose of the drug speedily forces the heart into fatal systole, but a minimum lethal or so-called therapeutic dose causes a slow action of the heart with prolongation of the diastole. During this prolonged diastole two or three auricular contractions overdistend the ventricle, which then empties itself with all the force it can still command. The contractility of the heart is not destroyed, but it is exhausted, and requires a more than usually powerful stimulant to rouse it to action. Rhythmic contractions occur spontaneously at long intervals under the influence of overdistention, even during prolonged standstill in diastole the ventricle can still be made to contract perfectly by mechanical irritation, and contractility only finally disappears when, after a long period of suspended action, the overdistended ventricle slowly and finally empties itself, shrinking to normal or smaller than normal dimensions.¹ Such a heart affords a typical example of a heart dying from exhaustion, the cause of which is not far to seek. Forced into increased energy in its movements, without any corresponding improvement in its metabolism, the heart has been compelled to draw upon its reserve, and when this fails death from exhaustion speedily follows. When death occurs in fatal systole after the administration of *strophanthus*, the cardiac muscle is found to be acid and to be so profoundly modified that it passes at once into a state indistinguishable from that of *rigor mortis*,—it is fatally poisoned. On the other hand, when a minimum lethal dose is administered the contractility of the heart is not abolished, and the myocardium still remains neutral or alkaline to the last.²

It has been claimed that *strophanthus* is not cumulative. As we have just seen, it may be injurious or even fatal without warning, and from this point of view there may be worse things than the warning we get of approaching saturation from those symptoms we are accustomed to ascribe to accumulation.

It has also been claimed that the absence of any action on the arterioles is to be reckoned to the advantage of *strophanthus* in those numerous cases in which vascular stimulants require to be conjoined with *digitalis* to prevent any untoward rise of blood-pressure. But apart from those evils already referred to, which are caused by this absence of action on the arterioles, we know that though improvement in the cardiac metabolism is the one thing needful in all cases of heart-failure, it is of paramount

¹ Fraser, *op. cit.*, vol. xxxvi., part 2, p. 419.

² *Ibid.*

importance in the class of cases just alluded to, because in them the heart-failure is due to the inability of the heart to cope unaided with the obstacles opposed to the exercise of its function. The employment in such a case of a drug like *strophanthus*, whose action is to stimulate and exhaust the reserve energy of the heart, must tend still further to enfeeble that organ, and persistence in its use must be most damaging to the integrity of the organism. On the other hand, the judicious combination of vascular stimulants with so powerful a cardiac stimulant as *digitalis* enables us so to regulate the blood-pressure as to keep it equable and efficient throughout the whole cardiac cycle, to the manifest advantage of the cardiac metabolism, and this, too, without any risk of the blood-pressure ever becoming so high as to be injurious.

The action of *strophanthus* is thus, like that of all its congeners of the *Apocynaceæ*, that of a cardiac poison, and not a cardiac tonic. In large doses—though from the energy of the drug such doses may be really small—it forces the heart into a fatal systole. In smaller doses it stimulates the heart to increased action, and by calling on its reserve of energy without improving its metabolism it causes death in diastole from exhaustion, and the more feeble the heart is the greater the risk attending this peculiar action. *Strophanthus* may occasionally be of use in cases of ruptured compensation, but any assistance which it gives is at the expense of the cardiac reserve, and the patient is only saved from serious disaster by the benefit he has derived from rest, warmth, and nutritious food,—that is, by the improvement in his environment generally.

Strophanthus is thus at all times an uncertain and dangerous drug to employ, and one entirely unworthy of being called a remedy.

It is quite otherwise with *digitalis*. This drug does not act by calling on the reserve of cardiac energy; but by improving the metabolism of the organism generally, and especially of the myocardium, it adds to this reserve, and aids any improvement in the environment, not only to tide over a temporary disability, but also to restore the myocardium to such a condition of comparative health as will enable it to withstand all the deteriorating influences to which it may be exposed.

It is difficult to conceive a greater contrast than that which subsists between the action of these two drugs, and the more carefully the actions of both are considered, the more markedly these differences will be found to be accentuated.

